AVAC
AIDS Vaccine Advocacy Coalition
Advocacy to accelerate ethical research & global delivery of AIDS Vaccines

July 29, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
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Re: Critical Path Initiative, **Docket No. 2004-N-0181**; 69 Fed. Reg. 21839, April 22, 2004

To the Food and Drug Administration:

The AIDS Vaccine Advocacy Coalition (AVAC) is pleased to submit these comments to identify pressing scientific or technical hurdles, along with solutions, in medical product development as part of FDA's Critical Path Initiative (Initiative).[1] AVAC is a volunteer and nonprofit public interest organization dedicated to ethical research and global delivery of vaccines to fight the AIDS pandemic. Along with others, we submitted preliminary comments for FDA's Science Board meeting held on April 22, 2004 when it first reviewed the Critical Path report,[2] and we request that FDA continue to take those preliminary comments into account while the Initiative moves forward. We support the FDA's Initiative program to remove barriers that prevent innovative medical therapies from reaching patients while maintaining high safety standards.

Identification of Scientific Hurdles/Problems/Opportunity

In response to the announcement to identify and solve specific problems meeting the Initiative goals, we request that FDA place directed research and planning for vaccine adjuvants high on the list of opportunities that will be funded and supported by the Agency's program. The lack of support for adjuvant research, regulatory approach, clinical test guidelines and basic science knowledge inhibit progress toward testing and eventual licensing of significant vaccines. Because not enough is known as to either the safety or the immune stimulating potential of adjuvants, the proposed research and other support should focus on solving both of these problems. We use the term adjuvant in the broadest sense to include any "substance that when incorporated into a vaccine formulation acts generally to accelerate, prolong, or enhance the quality of specific immune responses to vaccine antigens,"[3]

[1] FDA first announced the Critical Path Initiative on March 16, 2004 by publishing its report, "Innovation/Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products," and calling for identification of a Critical Opportunities List for improved medical product development efficiency. http://www.fda.gov/oc/initiatives/criticalpath/
[2] http://www.fda.gov/ohrms/dockets/ac/04/slides/4039s1.htm A copy of AVAC's earlier comments is attached.
[3] "Adjuvants in HIV Vaccine Research," Vogel FR, Vaccine and Prevention Research Program, Division of AIDS, National Institute of Allergy and Infectious Diseases, http://www.niaid.nih.gov/daids/vaccine/pdf/adjuvants.pdf

including but not limited to mineral salt or gel-type chemical compounds such as aluminum based adjuvants, particulate adjuvants, microbial derivatives, genetic materials such as cytokines or GM-CSF or inert vehicles. Adjuvants may be used to present antigen to the immune system, stimulate immune response, or increase the trafficking or bioavailability of the vaccine to the proper cell type, cellular compartment or presentation pathway.

Interest in the potential for adjuvants is driven by the need for and the complexity of vaccine research to prevent or mitigate the most serious global infectious diseases – AIDS, malaria, tuberculosis, each of them responsible for millions of deaths each year. Either as a prevention aid or with vaccine therapy, adjuvants also hold potential to improve vaccines for many cancers, provide dose-sparing effects in combination childhood immunizations or combat allergies.[4] Recently, NIAID and others identified adjuvant research as a priority but untapped area of inquiry necessary to advance the nation's biodefense programs.[5] This Critical Path Opportunity, therefore, has wide ranging and important application.

Marshalling the immune response necessary to attack any of these illnesses may be insufficient based on the effect of an unaided vaccine compound(s). Vaccines in many preclinical and clinical phase studies today are not whole killed or attenuated versions of the pathogens they seek to overcome and must use indirect mechanisms to induce sufficient response to complex and/or mutating proteins and genetic materials. In some cases, malaria, for example, the adjuvant component may be especially critical.[6] So far, inadequate potency or other deficiencies in immune response are the result in new vaccine testing.[7] A pressing need exists to supplement the effects of many candidate vaccine substances. Despite several decades of research interest, there is currently only one adjuvant licensed for use with human vaccines in the United States and one other in Europe while numerous compounds

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[4] http://www.cancer.gov/newscenter/benchmarks-vol3-issue1/page2; see also "Progress in Immunologic Adjuvant Development: 1982-2002" in The Jordan Report, 20th Anniversary, Accelerated Development of Vaccines (2002), p. 41 http://www.niaid.nih.gov/dmid/vaccines/jordan20/jordan20_2002.pdf

[5] Summary of the NIAID Expert Panel on Immunity and Biodefense, June 17, 2002, p.2; http://www.niaid.nih.gov/publications/pdf/biodimmunpan.pdf The Panel stated: "More basic information is needed on the cells that are affected by adjuvants and on the innate signaling pathways triggered in those cells. Methods are also needed to optimize adjuvanticity by targeting vaccine antigens to appropriate antigen presenting cell (APC) types, such as dendritic cells or macrophages; by targeting particular intracellular APC compartments for optimal antigen presentation to T cells; and by inducing appropriate APC maturation steps to optimize the stimulation of T cells, activate antibody production, and induce immune memory. Research should focus on the molecular mechanisms responsible for optimal antigen delivery and adjuvant activity in order to learn generalizable principles applicable to many vaccine candidates" See also http://www.niaid.nih.gov/biodefense/research/strategic.pdf An interesting paper on signaling pathways was recently published: Hoebe1 K, Janssen EM ,Kim SO, Alexopoulou L, Flavell RA, Han1J & Beutler B (2003) "Upregulation of costimulatory molecules induced by lipopolysaccharide and double-stranded RNA occurs by Trif-dependent and Trif-independent pathways," *Nature Immunology* **4**, 1223 – 1229. http://www.scripps.edu/newsandviews/e_20031124/beutler.html

[6] "Creating a malaria vaccine does not only involve discovering the optimal antigens; it is also important to enhance the immune response towards those antigens through adjuvants, especially since adjuvants are usually required with non-living vaccines. Studies have shown that one of the main determinants of protection against malaria may be the adjuvant vehicle. The adjuvants may be essential in influencing the specificity and isotype of the desired antibodies." http://www.brown.edu/Courses/Bio_160/Projects1999/malaria/vacc.html; http://www.niaid.nih.gov/dmid/malaria/malariavac.htm

[7] See, e.g. Emini EA and Koff WC (2004) "Developing an AIDS Vaccine:Need, Uncertainty, Hope," *Science* **304**, 5679, 1913-1914.

offer promise that has yet to be sufficiently or rationally explored.[8] It would seem that this medical product gap is precisely the kind of innovation stimulus that the Initiative was designed to address.

Government sponsored research into adjuvant testing and discovery has been underfunded. NIAID has solicited some initial research through its "broad agency announcement – innate immune receptor and adjuvant discovery" proposals,[9] and in a few other limited contexts, but this level of effort is insufficient and does not address cross-cutting application of adjuvant potential to a wide variety of vaccines. At the same time, private research by vaccine sponsors testing candidates for specific infections is constrained. Because many infection specific vaccine candidates in preclinical or preliminary phase I testing have not identified true correlates of protection or immune response and are in competition with other test vaccines, clinical trials shy away from testing additional adjuvants that may interfere with identification of effects from the primary test product. The relevant importance of specific quantitative as well as qualitative immune responses for vaccines is not well understood; as a result, vaccine trials rarely consider the additional or parallel testing of many potential adjuvant materials that are nevertheless assumed to be helpful in boosting the desired effect.

Vaccine sponsors or investigators who have large financial commitments and operational difficulties to navigate may lack direct access or means to essential intellectual property rights for further control over separate proprietary adjuvant materials in clinical settings or for broad combinations. A separate government impetus and support mechanism may mitigate this barrier to innovative medical therapy development.

Finally, U.S. investigators may be unclear as to the regulatory setting or expectations FDA feels it is necessary to use when balancing the safety and basic science problems involved in adjuvant development. The European Agency for the Development of Medical Products has recently issued its draft Guidelines on Adjuvants in Vaccines for consultation, [10] but U.S. based regulatory guidance for safety, efficacy or formulation is unclear as well as testing considerations in combinations. FDA worked with others to scope some of the safety issues involved over 10 years ago.[11]

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[8] "Beginning in the early 20th century, researchers experimented with a wide variety of organic and inorganic compounds including aluminum salts, mineral oil, and killed mycobacteria to improve the immunogenicity of vaccines. These first empirical studies demonstrated the adjuvant activity of many substances, but several products also elicited significant local and systemic adverse reactions that precluded their use in human vaccine formulations. Alum adjuvant, first described in 1926, remains the only immunologic adjuvant used in human vaccines licensed in the United States. Since the advent of modern immunology twenty years ago, hundreds of natural and synthetic compounds have been evaluated as vaccine adjuvants. After extensive safety and toxicity testing, many of these novel adjuvants have proven to be acceptable for clinical evaluation. During the same time, investigations into the mechanisms of action of adjuvants have increased. Today, a major goal of adjuvant research is to apply the increased understanding of basic immunobiology to adjuvant development. Improved understanding of adjuvant mechanisms of action will provide a basis for the rational selection of adjuvants for use with new vaccines." A Compendium of Vaccine Adjuvants and Excipients (2nd Edition) Vogel FR, Powell MF, and Alving CR http://www.niaid.nih.gov/daids/vaccine/pdf/compendium.pdf

[9] http://grants.nih.gov/grants/guide/notice-files/NOT-AI-03-055.html; see also adjuvanticity in innate immune activation http://grants.nih.gov/grants/guide/rfa-files/RFA-AI-04-023.html

[10] http://www.emea.eu.int/pdfs/human/veg/001703en.pdf

[11] Goldenthal KL, Cavagnaro JA, Alving CR, Vogel FR (1993) "Safety evaluation of vaccine adjuvants" National Cooperative Vaccine Development Working Group. *AIDS Res Hum Retroviruses* **9**:S45-S49.

Solutions

FDA posed a number of salient questions for arriving at solutions for the hurdles/opportunities: Is there a plan of basic scientific research to endorse? Would FDA guidance be appropriate? What are the time frames? What role should FDA play as direct actor to conduct research or as a convenor of stakeholders?

The problems and hurdles facing adjuvant research are multifactorial, involving basic science problems, regulatory uncertainty, science planning and economic arrangements. Because an integrated approach is necessary, we request that FDA exercise its role first as a stakeholder convenor and assemble representatives of vaccine programs and constituencies to air these barriers together. Public interest nonprofit organizations should be included in those discussions. We do expect and further request that the outcome of that effort may result in a significant direct role for FDA to conduct or sponsor research, and, certainly, to articulate a clear regulatory path for licensing additional adjuvants, harmonized with and supportive of the requirements of other jurisdictions.[12]

AVAC welcomes a chance to discuss these issues further with FDA representatives in person or to offer assistance convening stakeholders if that would be helpful. By discussing adjuvants in particular in these comments, we do not mean to diminish the importance of other worthwhile projects the Initiative might address such as manufacturing quality, safety markers or indicators of vaccine efficacy. We limited our remarks to the topic of adjuvants based on practical considerations. Please contact Mitchell Warren at tel: 212/367-1084 or by email at mitchell@avac.org if you have any questions regarding this letter. We look forward to hearing from you.

Very truly yours,

Mitchell Warren
Executive Director, AVAC

Michael Powell
President, AVAC

CC: Ms. Lisa Rovin, FDA
Mr. Richard Klein, FDA
Dr. Jan Johannessen, FDA
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[12] In AVAC's April 13, 2004 letter to the Science Board, we requested that FDA work closely with regulatory agencies in developing countries to increase and support their ability to approve products when new FDA Initiative tools are used. A recent article (Coplan PM, Mitchnick M, Rosenberg ZF (2004) "Regulatory Challenges in Microbicide Development" *Science* **304**, 5679, 1911-1912) sets out 5 steps to remove rate-limiting regulatory hurdles. We endorse and agree with those 5 principles as FDA moves forward with the Initiative.